Evidence for altered α-adrenoreceptor responsiveness after a single bout of maximal exercise

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Convertino, Victor A. Evidence for altered α-adrenoreceptor responsiveness after a single bout of maximal exercise. *J Appl Physiol* 95: 192–198, 2003. First published April 4, 2003; 10.1152/japplphysiol.00123.2003.—We studied hemodynamic responses to α- and β-receptor agonists in eight men to test the hypothesis that adrenoreceptor responsiveness is altered within 24 h of the performance of maximal exercise. Adrenoreceptor responsiveness was tested under two experimental conditions (with and without maximal exercise). Adrenoreceptor tests were performed 24 h after each subject performed graded upright cycle ergometry to volitional exhaustion. The 2 test days (experimental conditions) were separated by at least 1 wk, and the order of exercise and no-exercise conditions was counterbalanced. Steady-state graded infusions of phenylephrine (PE) and isoproterenol (Iso) were used to assess α- and β-adrenoreceptor responsiveness, respectively. Slopes calculated from linear regressions between Iso and PE doses and changes in heart rate, blood pressure, and leg vascular resistance for each subject were used as an index of α- and β-adrenoreceptor responsiveness. The slope of the relationship between heart rate and Iso with maximal exercise was $1,773 \pm 164$ beats·μg^{-1}·kg^{-1}·min^{-1} compared with $1,987 \pm 142$ beats·μg^{-1}·kg^{-1}·min^{-1} without exercise ($P = 0.158$), whereas the slopes of the relationship between vascular resistance to Iso were -438 ± 123 peripheral resistance units (PRU)·μg^{-1}·kg^{-1}·min^{-1} with maximal exercise and -429 ± 105 ·μg^{-1}·kg^{-1}·min^{-1} without exercise ($P = 0.904$). Maximal exercise was associated with greater ($P < 0.05$) vascular resistance (15.1 ± 2.8 PRU·μg^{-1}·kg^{-1}·min^{-1}) and mean arterial blood pressure (15.8 ± 2.1 mmHg·μg^{-1}·kg^{-1}·min^{-1}) responses to PE infusion compared with no exercise (9.0 ± 2.0 PRU·μg^{-1}·kg^{-1}·min^{-1} and 10.9 ± 2.0 mmHg·μg^{-1}·kg^{-1}·min^{-1}, respectively). These results provide evidence that a single bout of maximal exercise increases α₁-adrenoreceptor responsiveness within 24 h without affecting β-cardiac and vascular adrenoreceptor responses.

autonomic function; sympathetic; heart rate; blood pressure; baroreflex; vascular resistance

THE INABILITY TO INCREASE peripheral vascular resistance during conditions of central hypovolemia has been associated with orthostatic hypotension and intolerance (1). Performance of a single bout of graded exercise designed to elicit maximal effort has ameliorated orthostatic hypotension and/or intolerance in human subjects whose blood pressure regulatory mechanisms have been compromised (10–12, 15, 21). Mechanisms associated with improved orthostatic responses after maximal exercise include increased reserve for eliciting baroreflex-mediated peripheral vascular resistance (11, 12), although the mechanism(s) underlying this enhanced vasoconstrictive response are unclear.

One mechanism that might contribute to increased reserve for peripheral vasoconstriction is elevated sympathetic nerve activity as indicated by elevated plasma norepinephrine (NE) levels elicited during an orthostatic challenge 24 h after maximal exercise (11). However, increased peripheral vasoconstriction during orthostatic stress has been reported 24 h after maximal exercise in the absence of elevated plasma norepinephrine, suggesting that elevated sympathetic activity may not be necessary to elicit improved vasoconstrictive capacity (12). These latter results suggest the possibility that increased α- and/or reduced β-adrenergic receptor responsiveness of vascular smooth muscle may contribute to greater vasoconstrictive reserve. The notion that exercise might increase vasoconstrictive responses through alterations in adrenergic receptors is not without precedent. β-Adrenergic sensitivity was increased during relative inactivity when circulating catecholamines were chronically low (8, 17) and was reduced during relative activity when circulating catecholamines were chronically high (2). Similarly, there is evidence that increased α-adrenergic sensitivity was associated with chronic exercise training (14, 20). However, we are unaware of any data that describe alterations in adrenergic receptor function within 24 h of the performance of intense physical exercise; such information might provide a possible explanation for increased vasoconstrictive reserve. In the present investigation, we measured heart rate (HR) and peripheral vascular resistance responses to adrenergic agonists in human subjects 24 h after they performed graded cycle ergometry designed to elicit volitional exhaustion to test the hypothesis that maximal exercise would acutely increase α- and/or reduce β-adrenoreceptor responsiveness (i.e., sensitivity).

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METHODS

Subjects. After being informed of all procedures and risks, eight healthy, normotensive, nonsmoking men with mean age of 27 ± 2 (SE) yr (range 20–35 yr), height of 177 ± 4 cm (range 160–180 cm), and weight of 81.5 ± 4.1 kg (range 61.4–90.9 kg) gave their written consent to serve as subjects for this investigation. All experimental procedures and protocols were approved by the Human Research Review Boards at Brooks Air Force Base and the US Army Institute of Surgical Research. Selection of subjects was on the basis of results of a screening evaluation comprised of a detailed medical history, physical examination, blood chemistry analysis, urinalysis, and electrocardiogram. Subjects were familiarized with all laboratory personnel, procedures, and protocols during an orientation session conducted before the study.

General protocol. On a random basis, each subject completed two experimental treatments that entailed tests of adrenoreceptor responsiveness *1*) 24 h after performance of an exercise test designed to elicit maximal effort and *2*) during a no-exercise (control) session. A minimum of 1 wk intervened between the two experimental test sessions. With the exception of the maximal exercise bout, the same protocol was followed on the no-exercise experimental day. Subjects maintained their normal sleep pattern, and they refrained from exercise and abstained from caffeine and other autonomic stimulants such as prescription and non-prescription drugs for at least 48 h before each experimental protocol. The subjects were instructed to control their physical activity to sitting and minimal walking for both the exercise and control treatments during the 24 h before data collection periods. Meal time and composition during the 24 h preceding each experimental protocol were duplicated as closely as possible. All subjects arose at their usual awakening time, ranging from 0600 to 0700, on the day of each experimental protocol, and ate their usual breakfast. Both experimental protocols were initiated at the same time of day. Continuous HR was measured from an electrocardiogram and beat-by-beat systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures were measured noninvasively by the Finapres finger cuff blood pressure monitoring device. These tests were conducted over a period of ~2 h on each test day.

Maximal exercise. A graded exercise test to volitional fatigue was performed in the upright posture by each subject 24 h before tests of adrenoreceptor responsiveness utilizing a Quinton (model 845B) electronically braked cycle ergometer. The test consisted of continually graded work intensities at a pedaling frequency ranging from 60 to 70 rpm. The work rate for the initial 4 min was 200 kpm/min, after which the work rate was increased each minute by 100 kpm/min increments until the subject reached volitional exhaustion. Subjects were verbally encouraged to achieve a maximal effort.

Measurements of adrenoreceptor responsiveness. After 30 min of supine rest, baseline measures of HR, MAP, and leg blood flow were made. Leg blood flow was measured with the left leg slightly elevated (~10 cm) at the ankle by using venous occlusion plethysmography with a dual-loop mercury-in-Silastic strain gauge placed around the left calf at the point of maximal circumference. Venous outflow from the calf was prevented by the placement of a cuff around the thigh just above the knee by using an occlusion pressure of +60 mmHg. Arterial occlusion to reduce blood flow to the foot was applied by an ankle cuff inflated at a pressure of +250 mmHg. After ankle cuff inflation for 1 min, six 10-s occlusions were repeated during the final 2 min of each test condition, and the average of the six measurements repre-

sented the flow for that test condition. The relative change (percent) in strain-gauge length over 10 s was quantified as a volume of blood per unit time, i.e., flow. MAP was calculated by dividing the sum of SBP and twice DBP by three. An index of leg vascular resistance (LVR) was calculated by dividing MAP by average flow during the final 2 min of each adrenoreceptor-agonist condition and expressed as peripheral resistance units (PRU; in mmHg·min·100 ml·ml^{-1}). After baseline measurements, graded dose infusions of an α-adrenoreceptor agonist followed by graded dose infusions of a β-adrenoreceptor agonist were performed through a left arm venous catheter with isotonic saline as a vehicle. Each infusion interval was 5 min in duration to establish steady state and allow adequate time for all measurements. The protocol and dosages of adrenoreceptor agonists were determined by laboratory experience to produce safe but significant physiological responses (4, 5, 8). The total volume infused was <50 ml. A recovery period of at least 30 min was allowed between the two agonist infusion protocols to allow hemodynamic measurements to return to preinfusion resting levels. During both infusion protocols, constant monitoring of beat-to-beat MAP and HR was performed, and leg blood flows were measured at each infusion level.

α_1-Adrenoreceptor responsiveness. Graded infusion of the α_1-adrenoreceptor agonist phenylephrine (PE) was used to assess the responsiveness of these vascular receptors. PE was infused at three graded constant rates of 0.25, 0.50, and 1.00 μg·kg^{-1}·min^{-1}. An elevation of SBP of 20 mmHg above or reflex reduction in HR of 20 beats/min below resting were predetermined end points for test termination. No tests were terminated with the use of these criteria. The response of α_1-adrenoreceptors was assessed by relating the PE dose with elevations in LVR and MAP. Because the relationships between PE doses and LVR are linear (4, 5, 8), the slopes describing these relationships were used to represent an index of α_1-adrenoreceptor responsiveness. Differences in slopes (ΔLVR/ΔPE or ΔMAP/ΔPE; where Δ is change) between the exercise and control conditions were compared by analyzing the least squares linear estimates generated by each subject. The relationship between the change in MAP caused by graded infusion of PE and the reflex change in HR (ΔHR/ΔMAP) was calculated and used to provide an assessment of integrated arterial-cardiac baroreflex function.

β-Adrenoreceptor responsiveness. After HR, SBP, and DBP returned to resting levels after PE infusions, infusions of isoproterenol (Iso) were used to assess the responsiveness of β_1- and β_2-adrenoreceptors. Iso was infused at three graded constant rates of 0.005, 0.01, and 0.02 μg·kg^{-1}·min^{-1}. An elevation of HR by 35 beats/min above resting was the predetermined end point for test termination. No tests were terminated using this criteria. Linear regression relationships were then constructed relating the increase in HR and the decrease in LVR to the dose of Iso. The slopes describing the linear stimulus-response relationship between the dose of Iso and HR and LVR provided a measure of the systemic responsiveness of β_1- and β_2-adrenoreceptors, respectively. Differences in slopes (ΔHR/ΔIso or ΔLVR/ΔIso) between the exercise and control conditions were compared by analyzing the least squares linear estimates generated by each subject.

Plasma catecholamine measurements. Ten milliliters of blood were taken without stasis from the left arm catheter before and immediately after the third infusion level of PE and Iso to determine the response of NE and epinephrine (Epi). Immediately after each withdrawal, whole blood was taken from the syringe, transferred to a chilled tube containing sodium EDTA, and centrifuged at 2,000 *g* for 20 min at 4°C. Immediately after centrifugation, the plasma was ali-

quoted for NE and Epi and was stored frozen until analyses were performed. Plasma NE and Epi concentrations were measured by high-performance liquid chromatography (Waters, Milford, MA) according to standardized procedures (4, 5, 8).

Statistics. Standard descriptive statistics were performed on each of the response variables of interest with results presented as means ± SE. Standard paired *t*-test statistics were used to compare mean slopes of the dose-response relationships between drug infusions and HR, blood pressures, and LVR with and without maximal exercise, and for comparison of baseline HR and blood pressures. Repeated-measures analysis of variance was performed to determine differences between measurements in blood pressures, NE, and Epi between exercise and control treatments and across drug infusions. Exact *P* values were calculated for each independent effect and reflect the probability of observing the measured effect or one larger given only random error. All statistical tests were based on eight subjects. Error bars presented in figures reflect simple SEs around means, but they do not reflect variation specific to the experimental design or the variability associated with the statistical tests.

RESULTS

Exercise bout. Final work rate at volitional fatigue averaged $1{,}571 \pm 60$ kpm/min and was attained after a mean time of 17.4 ± 0.6 min. HR, SBP, and DBP at termination averaged 186 ± 3 beats/min, 182 ± 2 mmHg, and 77 ± 3 mmHg, respectively.

Baseline measurements and general observations. Baseline HR and blood pressures just before Iso or PE infusion were virtually unaltered by maximal exercise compared with the control condition (Table 1). There were no junctional rhythms in any of our eight subjects during infusion of either adrenergic agonist.

α-Adrenoreceptor responsiveness. Figure 1 represents the regressions calculated from the mean ($\pm$ SE) responses of LVR and MAP at each PE level with and without exercise. The average slope of the dose-response relationship between PE and LVR (Fig. 1, *top*) was greater ($t = 2.515$, df = 1, $P = 0.040$) 24 h after maximal exercise (15.1 ± 2.8 PRU$\cdot\mu$g$^{-1}\cdot$kg$^{-1}\cdot$min^{-1}) than the control condition (9.0 ± 2.0 PRU$\cdot\mu$g$^{-1}\cdot$kg$^{-1}\cdot$

Table 1. *Baseline heart rate and blood pressures before isoproterenol and phenylephrine infusions 24 h after maximal exercise and without exercise (control)*

	Isoproterenol Test	Phenylephrine Test
Heart rate, beats/min		
Control	59 ± 2	58 ± 1
Exercise	60 ± 2	60 ± 2
Systolic blood pressure, mmHg		
Control	125 ± 2	124 ± 2
Exercise	125 ± 3	121 ± 2
Diastolic blood pressure, mmHg		
Control	70 ± 3	68 ± 2
Exercise	74 ± 3	71 ± 2
Mean arterial blood pressure, mmHg		
Control	90 ± 2	88 ± 2
Exercise	91 ± 2	87 ± 2

Values are means ± SE for 8 subjects. Statistical analyses revealed no statistical differences.
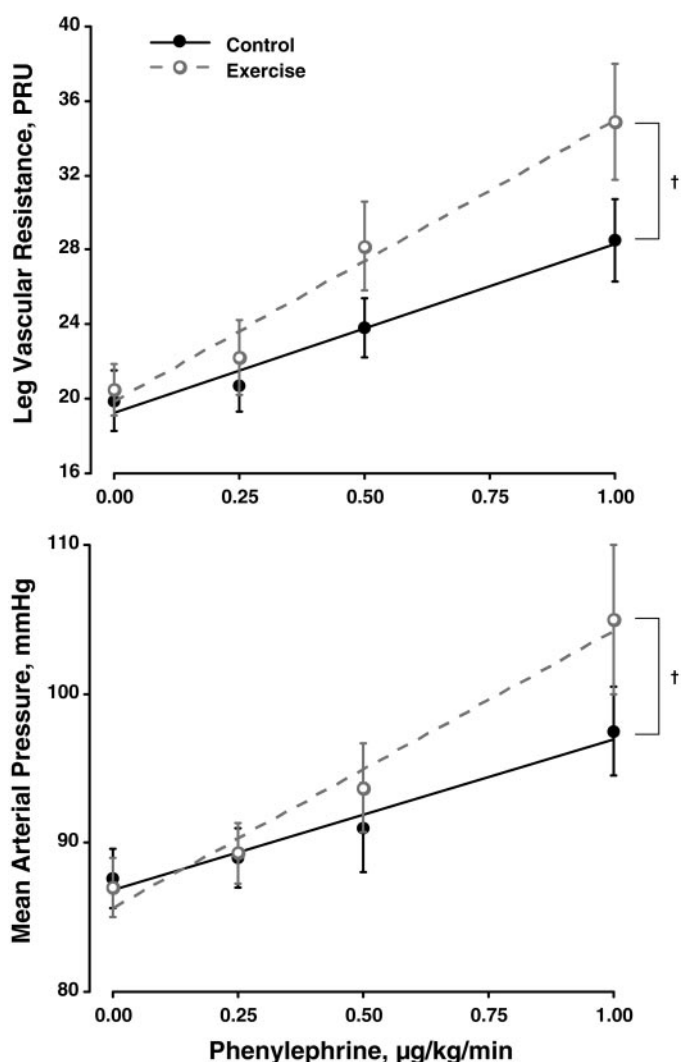

Fig. 1. Dose-response relationships between phenylephrine (PE) and leg vascular resistance (*top*) and mean arterial blood pressure (*bottom*) 24 h after the subjects completed a single bout of maximal exercise (○ and dashed lines) and without exercise (control; ● and solid lines). Values are means ± SE. Linear regressions are calculated from mean leg vascular resistance and mean arterial blood pressure values of 8 subjects. For leg vascular resistance, the linear equation for mean control data is $y = 9.0x + 19.3$ ($r^2 = 0.975$) and for mean exercise data is $y = 15.1x + 19.8$ ($r^2 = 0.976$). For mean arterial blood pressure, the linear equation for mean control data is $y = 10.1x + 86.9$ ($r^2 = 0.968$) and for mean exercise data is $y = 18.5x + 85.7$ ($r^2 = 0.974$). PRU, peripheral resistance units. †Differences in slopes of responses, $P < 0.05$.

min^{-1}). Similarly, the average slope of the dose-response relationship between PE and MAP (Fig. 1, *bottom*) increased ($t = 2.438$, $P = 0.045$) in all eight subjects 24 h after maximal exercise (15.8 ± 2.1 mmHg$\cdot\mu$g$^{-1}\cdot$kg$^{-1}\cdot$min^{-1}) compared with the control condition (10.9 ± 2.0 mmHg$\cdot\mu$g$^{-1}\cdot$kg$^{-1}\cdot$min^{-1}).

β-Adrenoreceptor responsiveness. Blood pressures were statistically indistiguishable between exercise and control conditions at baseline and during infusion for the Iso test (Table 2). Figure 2 represents the regressions calculated from the mean ($\pm$ SE) responses of HR and LVR at each Iso level with and without

Table 2. *Blood pressure responses at baseline and three levels of isoproterenol infusion 24 h after maximal exercise and without exercise (control)*

| | Baseline | Isoproterenol, $\mu g \cdot kg^{-1} \cdot min^{-1}$ | | |
		0.005	0.010	0.020
Systolic blood pressure, mmHg				
Control	125 ± 2	127 ± 5	136 ± 6	135 ± 4
Exercise	125 ± 3	126 ± 3	133 ± 4	138 ± 6
Diastolic blood pressure, mmHg				
Control	70 ± 3	65 ± 3	53 ± 4	52 ± 3
Exercise	74 ± 3	64 ± 3	54 ± 3	53 ± 3
Mean arterial blood pressure, mmHg				
Control	90 ± 2	86 ± 3	81 ± 3	80 ± 3
Exercise	91 ± 2	85 ± 2	80 ± 2	82 ± 2

Values are means $\pm$ SE for 8 subjects. Statistical analyses revealed no statistical differences.

exercise. The dose-response relationships between Iso and HR were superimposed (Fig. 2, *upper*) with average slope for the exercise condition equal to $1,773 \pm 164$ beats $\cdot \mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$ and for the control condition equal to $1,987 \pm 142$ beats $\cdot \mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$ ($t = 1.581$, df $= 1$, $P = 0.158$). Similarly, the average slope of the dose-response relationship between Iso and LVR (Fig. 2, *bottom*) was statistically similar ($t = 0.125$, $P = 0.904$) 24 h after maximal exercise (-438 ± 140 PRU $\cdot \mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$) to that of the control condition (-429 ± 125 PRU $\cdot \mu g^{-1} \cdot kg^{-1} \cdot min^{-1}$).

Catecholamine responses. Compared with preinfusion baseline, plasma NE was increased by Iso infusion and decreased by PE infusion [$F(2,14) = 24.40$, $P < 0.0001$] both during exercise and control conditions. Plasma Epi was not altered with either Iso or PE infusion [$F(2,14) = 0.933$, $P = 0.417$]. There were no statistical differences in plasma NE [$F(1,7) = 0.238$, $P = 0.641$] and Epi [$F(1,7) = 0.049$, $P = 0.831$] concentrations between exercise and control treatments at baseline rest and during all infusion conditions (Fig. 3).

Cardiac baroreflex response. The ΔHR/ΔMAP response to PE was decreased ($t = 2.257$, df $= 1$, $P = 0.059$) in all 8 subjects 24 h after exercise (-1.0 ± 0.2) compared with control (-2.7 ± 0.8).

DISCUSSION

The major finding of this study was that maximal exercise led to substantial increases in the vasoconstrictive response to α_1-adrenergic stimulation but that it had little effect on the HR and vasodilatory responses to a β-adrenergic agonist. The results of the present study also substantiated that baseline circulating NE and Epi were not altered by acute intense exercise. Spina and coworkers (20) demonstrated that the elevation in MAP from basal levels in response to a given dose of PE was significantly larger after than before exercise training, suggesting that chronically repeated exercise can induce an increase in α_1-adrenergic responsiveness. However, our data may be the

first to provide evidence that α_1-adrenoreceptor responsiveness can be selectively increased in healthy humans within 24 h of intense exercise.

In contrast to our findings, Spier and coworkers (19) reported no change in vascular (abdominal aorta) sensitivity to vasoconstrictor agonists, including PE, 24 h after a single bout of running exercise performed by rats on a motor-driven treadmill at 30 m/min (15° incline). This discrepancy between the findings of Spier et al. and the present study may simply reflect differences in the control of a conductance vessel (aorta) and resistance vessels controlling peripheral blood flow (calf). However, it is also possible that differences in
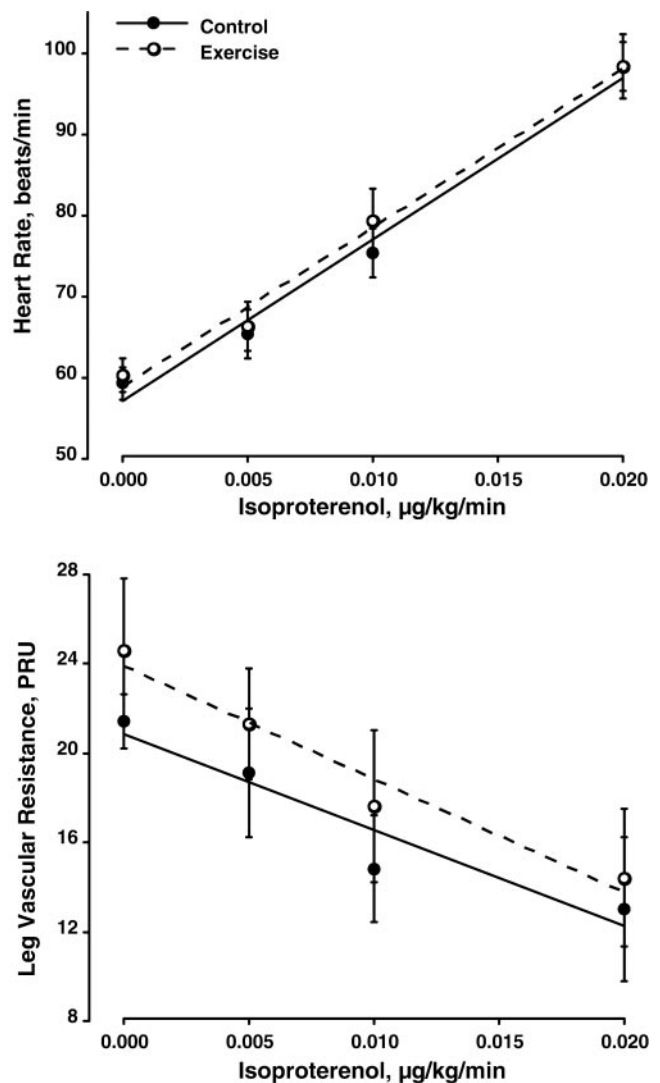

Fig. 2. Dose-response relationships between isoproterenol (Iso) and heart rate (*top*) and leg vascular resistance (*bottom*) 24 h after the subjects completed a single bout of maximal exercise (○ and dashed lines) and without exercise (control; ● and solid lines). Values are means $\pm$ SE. Linear regressions are calculated from mean heart rate and leg vascular resistance values of 8 subjects. For heart rate, the linear equation for mean control data is $y = 1,944x + 56.8$ ($r^2 = 0.986$) and for mean exercise data is $y = 1,960x + 58.6$ ($r^2 = 0.990$). For leg vascular resistance, the linear equation for mean control data is $y = -430x + 20.7$ ($r^2 = 0.908$) and for mean exercise data is $y = -508x + 23.8$ ($r^2 = 0.959$).
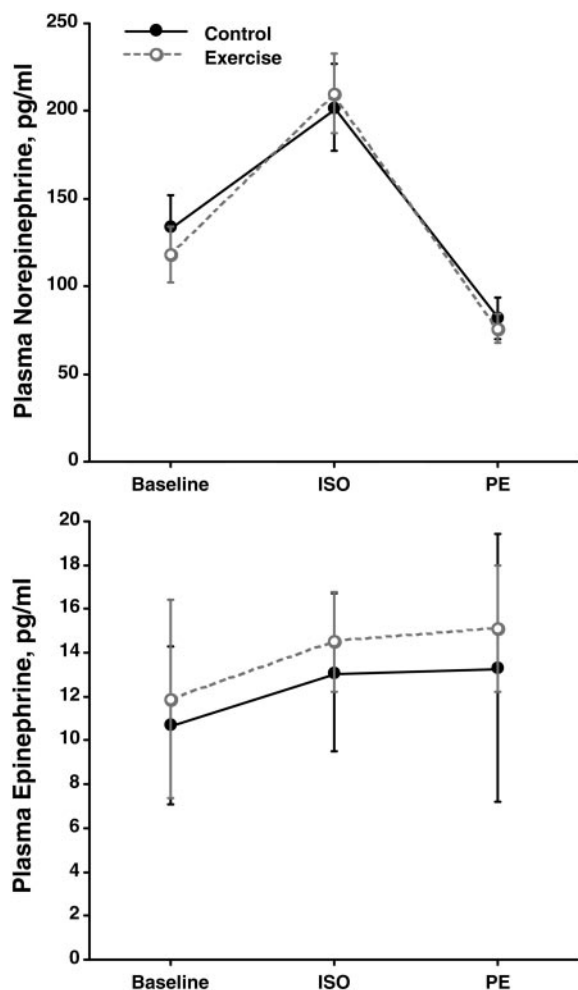
Fig. 3. Plasma concentrations of norepinephrine (*top*) and epinephrine (*bottom*) during baseline rest and at the end of Iso and PE infusions 24 h after the subjects completed a single bout of maximal exercise (○ and broken lines) and without exercise (control; ● and solid lines). Values are means ± SE. Compared with preinfusion baseline, plasma norepinephrine was increased by Iso infusion and decreased by PE infusion ($P = 0.0001$) under both exercise and control conditions.

vascular response to PE may reflect the importance of exercise intensity as a stimulus for inducing adrenergic receptor changes. Although the intensity of exercise relative to maximal capacity was not reported for this animal experiment, it is likely that the exercise intensity was well below maximal because the animals were able to exercise for 1 h. When α-adrenergic responsiveness was increased 24 h after exercise in either animals (3) or humans (present investigation), the intensity of exercise required maximal exhaustion. These comparisons may support the notion that a minimum threshold of exercise intensity is required to provide an adequate stimulus for inducing an increase in α-adrenergic receptor function.

Our laboratory previously reported increased or restored vasoconstrictive reserve and maximal peripheral vascular resistance during central hypovolemia (orthostatic stress) in subjects who performed maximal exercise at the end of exposure to bed rest (11) or were confined to a wheelchair (12). There are several possible mechanisms that might contribute to increased vasoconstriction induced by maximal exercise. Increased baroreflex sensitivity for control of peripheral vascular resistance might explain greater vasoconstriction in response to a given orthostatic challenge. However, this hypothesis is not supported by the observation that the slope of the baroreflex stimulus-response relationship for control of peripheral vascular resistance was not altered 24 h after maximal exercise (7). The notion that maximal exercise induced a hyperreactive vascular response through increased sympathetic nerve activity was initially supported by elevated plasma NE levels at the onset of presyncope 24 h after maximal exercise (11). However, increased peripheral vasoconstriction during orthostatic stress in the absence of elevated plasma catecholamines 24 h after maximal exercise does not support the hypothesis of a universal role for enhanced sympathetic response (12). The data from the present investigation support the notion that increased responsiveness of vascular α$_1$-adrenergic receptors may represent a common mechanism that could explain the previous observations of an increase in vasoconstrictive reserve induced by maximal exercise.

The absence of regular exercise in subject populations confined to bed rest or with autonomic dysfunctions was reported to be associated with chronically low circulating catecholamines and increased β-adrenergic receptor sensitivity (8, 17). In contrast, β-adrenergic receptor sensitivity was found to be reduced in the presence of elevated circulating catecholamines in individuals who participated in relatively high-level physical activity (2). Because vascular β$_2$-adrenoreceptors elicit vasodilation, the overall effect of reduced β$_2$-adrenoreceptor responsiveness accompanying intense physical activity (exercise) could produce a greater vasoconstrictive effect and provide, at least in part, an explanation for increased reflex-mediated vascular resistance reported 24 h after maximal exercise (11, 12). Consequently, we hypothesized that the performance of maximal exercise in the present investigation would lead to a decrease in β$_2$-adrenergic receptor response. Unexpectedly, we found that the β$_2$-adrenergic vascular response was unaltered 24 h after the performance of maximal exercise. Our results suggest that the ability to induce an attenuation of β-adrenergic receptor sensitivity with physical activity may require exposure to chronically repeated bouts of exercise.

It is clear that the capacity for peripheral vasoconstriction is an important determinant of regulating arterial blood pressure under conditions of central hypovolemia (1, 6, 16, 18). Because vascular α-adrenoreceptors elicit vasoconstriction compared with the vascular dilation mediated by β$_2$-adrenoreceptors, the overall effect of greater α$_1$-adrenoreceptor responsiveness in the absence of changes in β$_2$-adrenoreceptor responses could enhance vasoconstrictive reserve, especially under a condition of increased sympathetic

discharge during central hypovolemic challenge. The potential to increase the reserve capacity for elevations in peripheral vascular resistance could improve the capacity of the cardiovascular system to maintain adequate arterial blood pressure and cerebral perfusion during central hypovolemia.

The mechanism(s) of increased α_1-adrenoreceptor responsiveness observed 24 h after maximal exercise in the present study is unclear. Enhanced α_1-adrenoreceptor responsiveness observed in our subjects does not appear to be associated with increased sympathetic nerve activity because total circulating NE was not different between exercise and control conditions. However, the possibility of increases in adrenergic receptor number or sensitivity (affinity) is supported by data from animal models. Korzick and Moore (14) reported that greater myocardial α_1-adrenergic receptor number in exercised rats compared with sedentary rats was significantly correlated with the inotropic responsiveness of the heart to PE stimulation. More relevant to the our results, Cheng and coworkers (3) reported decreased number but increased affinity of α_2-binding sites in endothelium of thoracic aorta in rats after acute maximal exhaustive exercise. These animal studies provide support for the notion that exercise can alter α-adrenergic receptor function and that this effect can occur rapidly (within 24 h). Our data may be the first to demonstrate that rapid alterations in α_1-adrenergic receptor function occur in humans within 24 h of maximal exercise and may be associated with increased receptor number and/or receptor affinity.

Our experimental methology is not without limitations. We chose to use steady-state rather than bolus infusion of the agonists to measure important vascular resistance data which could not be obtained by a distribution-phase method. Despite our success of matching hemodynamic and catecholamine responses at baseline and during drug administration, interpretation of results on the basis of the use of systemic steady-state infusion of adrenergic agonists in human subjects is complicated by the presence of blood volume expansion and compensatory baroreflex responses to adrenergic stimulation. The expansion of blood volume that occurred 24 h after maximal exercise in our subjects (7) should have been associated with an attenuation of baroreflex-mediated vascular reactivity (22). However, the stimulus-response relationship for baroreflex control of peripheral vascular resistance was not different between the maximal exercise and control conditions in our subjects (7), suggesting that the sensitivity of reflex vasoaction was increased by maximal exercise. This observation is consistent with previous findings (10–12). A hypertensive stimulus induced by steady-state PE infusion would be expected to reflexly buffer vasoconstriction to a greater degree after maximal exercise when baroreflex control of peripheral vascular resistance is more sensitive. This could lead to an underestimation of the α_1-adrenoreceptor response observed in the present study. Because the hypertensive response to PE was greater 24 h after maximal exercise in the presence of a more sensitive baroreflex control of peripheral vascular resistance, it is unlikely that our interpretation of increased vascular reactivity was influenced by the limitation of steady-state infusion of PE. Finally, our interpretation of the reason for an absence of exercise effect on cardiac responses to Iso may be complicated by an attenuation of the arterial-cardiac baroreflex responsiveness in our subjects. Because the cardiac baroreflex was reduced by 60% 24 h after maximal exercise (7), we might expect a similar low response in the HR response to Iso for an equal change in MAP. Instead, the change in HR to Iso was similar after compared with before exercise, suggesting the possibility that we may have underestimated the effect of maximal exercise on the β_1-adrenoreceptor cardiac response.

Perspectives. The use of exercise as a potential treatment or countermeasure against development of orthostatic hypotension and intolerance has been long considered because of the recognized effect of physical activity on circulating blood volume and baroreflex functions (6). Because the capacity for vasoconstriction is associated with hypovolemic hypotension (1, 6, 16, 18), the identification of exercise that enhances control mechanisms underlying peripheral vascular smooth muscle contraction should provide an effective countermeasure. The data from the present investigation provide evidence that increased α_1-adrenergic receptor responsiveness may represent a mechanism by which acute maximal exercise acts to increase vasoconstrictive reserve and improve orthostatic tolerance (10–12, 15, 21). In contrast to our results, chronic submaximal exercise training is associated with increased peripheral vascular responsiveness to vasodilators and reduced sensitivity to the vasoconstrictor effects of NE, apparently due to alterations in endothelium-dependent mechanisms involving receptors other than α_1-adrenergic receptors (9). It should therefore not be surprising that submaximal exercise training failed to restore tolerance in orthostatically compromised humans (13). Taken together, the data from the present and past investigations support the notion that the adaptations associated with alterations in adrenergic receptor function are very specific to the specific stimuli of exercise intensity, frequency, and duration and alterations of other mechanisms associated with blood pressure regulation. Therefore, the desired outcomes of cardiovascular function will depend on carefully applied characteristics of the specific exercise.

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